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DATE MAILED: 09/11/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/589,777 | SUKHATME, VIKAS P. | |
| | Examiner | Art Unit | |
| | Natalie A Davis | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 January 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-4, 11-16, 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 35* is/are rejected.

7)☒ Claim(s) *1,3 and 4* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

## DETAILED ACTION

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

   I. Claim 1, drawn to an anti-angiogenic peptide, classified in class 530, subclass 300.

   II. Claims 2-4, 11-16, and 35, drawn to a mutated protein and a composition, classified in class 530, subclass 387.1.

   III. Claims 5-10, 32, and 33, drawn to an isolated polynucleotide, a host cell, and a process of producing a protein, classified in class 536, subclass 23.1.

   IV. Claim 17 and 22, drawn to a method for inhibiting angiogenic activity in mammalian tissue and inducing apoptosis, classified in class 435, subclass 7.1.

   V. Claims 18-21, and 23-25 drawn to a method of treating a disease in a patient, classified in class 424, subclass 192.1.

   VI. Claims 26-30, drawn to a process of providing a mammal with EM1, classified in class 424, subclass 93.21.

   VII. Claim 31, drawn to a method of isolating a polynucleotide, classified in class 435, subclass 91.1.

   VIII. Claim 34, drawn to an antibody, classified in class 530, subclass 387.1.

2. The inventions are distinct, each from the other because of the following reasons:

   a. Inventions I-VIII are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the products of Groups I-III and VIII may be used for a number of different processes that are very much unrelated. As indicated by the claims, the protein of Group II may not only be used in the method of Group V, but may also be used to isolate an antibody (Group VIII). Furthermore, the methods of Groups IV-VII may be practiced using various products and do not have to be used with the products of the above Groups. For example, the method of inducing

apoptosis (Group IV) may be may be practiced using another materially different apoptotic protein such as p53 and does not necessarily have to be used with the protein of Group II.

b. Inventions III (claims 32-33) and VII are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the invention of Group III can be chemically synthesized and does not necessarily have to be made by the process of group VII.

c. Inventions I-III and VIII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are structurally and functionally different, are drawn to structurally and functionally different molecules, each invention requires different reagents and steps to make and characterize them, or different methods of use that do not share common steps or reagents and rely on different endpoints. For example, a polynucleotide can be used to make a protein, but the protein can be extracted directly from cells and does not have to be derived from a nucleic acid sequence. A polynucleotide can be used directly for immunization and not just for making a protein. Likewise, polypeptide may be used to make a fusion protein and does not have to be used to isolate an antibody.

d. Inventions IV-VII are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions relate to methods but each method differs in method steps, modes of operation, reagents needed and serve different endpoints and

effects. For example, the method of isolating a polynucleotide is very different from inducing apoptosis.

3. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, divergent subject matter, and require different search strategies, restriction for examination purposes as indicated is proper.

4. Attorney Hogel on 9 March, 2001 left a voice mail message wherein a provisional election was made with traverse to prosecute the invention of Group II, claims 2-4, 11-16, and 35. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1, 5-10, and 17-34 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

***Information Disclosure Statement***

5. The information disclosure statement filed 16 August 2000 has been considered. A signed copy is attached hereto.

***Amendments***

6. Applicant's amendments to the specification filed 25 June 2001 are acknowledged. In addition, traversal of the telephonic election is acknowledged. The traversal is on the ground(s) that the inventions are not independent or distinct. Furthermore, that searching each group would not be a burden on the examiner. This is found to be persuasive and claim 1 will be examined as belonging to Group I.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-4, 11-16, and 35 are being examined as belonging to the elected Group II, while claims 5-10 and 17-34 are withdrawn from examination as being drawn to a non-elected invention.

***Specification***

7. The abstract of the disclosure is objected to because it is not in compliance with Rule 37 CFR 1.72(b). The content of a patent abstract should be such as to enable the reader thereof, regardless of his or her degree of familiarity with patent documents, to ascertain quickly the character of the subject matter covered by the technical disclosure and should include that which is new in the art to which the invention pertains. The abstract should be in narrative form and generally limited to a single paragraph within the range of 50 to 250 words. Correction is required. See MPEP § 608.01(b).

8. The application fails to comply with the sequence requirements of 37 C.F.R. 1.821-1.825, as claims 1, 3, and 4 do not have required SEQ ID NO:. According to 37 C.F.R. 1.821 a nucleotide and /or amino acid sequences are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Applicant must make the following corrections according to 37 C.F.R. 1.821 (d), which states: where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c), reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

### *Claim Rejections - 35 USC § 112*

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is drawn to isolated EM1, which comprises a mutated endostatin protein.

a. Recitation of "EM1" without delineation of the full name of the entity, which the abbreviation denotes is indefinite. For purposes of clarification it is suggested that the claims be amended at the first occurrence of the abbreviation to recite the full name.

Claim 35 is drawn to an isolated mutant, derivative, analog, or homolog of EM1.

c. It is indefinite in the recitation of " derivative, analog, or homolog" as the metes and bounds for what modifications of EM1 may constitute a derivative, analog, or homolog. A derivative is interpreted as being a fragment, mutation, or any modification to the protein, such as insertions, deletions, substitutions, addition of side groups, etc. Since these terms do not have a universally accepted meaning in the art and the exact meanings are not known, it is not clear as to what peptide would be a derivative, analog, or homolog of EM1.

10. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 35 recites the broad recitation an isolated mutant, derivative, analog, or homolog of the EM1, and the claim also recites the EM1 of claim 2 which is the narrower statement of the range/limitation.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir., 1988). They include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The elected claim is drawn to an isolated mutant, derivative, analog, or homolog of EM1.

The specification defines an analog of EM1 as a non-natural molecule substantially similar to either the entire EM1 molecule or a fragment or allelic variant thereof, and having the same biological activity. Analogs may include derivatives, as well as fragments, mutants, homologs, and allelic variants (p. 18). The specification defines a mutant as a polypeptide that includes any change in the amino acid sequence relative to the EM1 sequence and a mutation may include base changes, deletions, insertions, inversions, translocation, or duplications (p.17).

12. The claim as broadly interpreted is not enabled for the following reasons:

The specification provides no guidance or exemplification as how to make or select for a derivative, analog, or homolog to EM1 that retains the anti-angiogenic activity of EM1. Applicant has not enabled all of these types of proteins because it has not been shown that these polypeptides are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, conservative replacement of a single "lysine" reside at position 118 of acidic fibroblast growth factor by "glutamic acid" led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al., J of Cell Bio. 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cellular Biology 8:1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often

dramatically affect the biological activity and characteristic of a protein. Furthermore, the specification fails to teach what deletions, truncations, substitutions and mutations of the disclosed sequence can be tolerated that will allow the protein to function as claimed. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with reasonable expectation of success are limited. Certain positions in the sequence are critical to the three-dimensional structure/function relationship, and these regions can tolerate only conservative substitutions or no substitutions. Residues that are directly involved in protein functions such as binding will certainly be among the most conserved (Bowie et al. Science, 247:1306-1310, 1990, p. 1306, col.2). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to use any and all isolated mutant, derivative, analog, or homolog of EM1. Thus, one skilled in the art would not know how to practice the invention in its full breadth of scope because the specification provides no guidance as how to make or select for a derivative, analog, or homolog of EM1, which would retain the anti-angiogenic activity of EM1.

***Claim Rejections - 35 USC § 102***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 1 are rejected under 35 U.S.C. 102(b) as being anticipated by Oh, et al., (1995). The claims are drawn to an isolated anti-angiogenic peptide, wherein the C-terminus comprises the amino acid sequence SYIVLCIE.

Oh, et al., teach an amino acid sequence comprising the endostatin protein, which may be useful in the treatment of solid tumors, thus indicating its anti-angiogenic capabilities. Therefore, the prior art reference teaches the as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Natalie A. Davis whose telephone number is 703-308-6410. The examiner can normally be reached on M-F 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4315 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Natalie A. Davis
September 5, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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